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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MERTZ, PREMA MARIA

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,225	LEE ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/3/05, 10/28/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,9,12,15-18,23-29 and 37* is/are pending in the application.

4a) Of the above claim(s) *1-4,6,8,9,12,23-29 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/17/03*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group V (claims 15-18) in the reply filed on 10/3/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-4, 6, 8-9, 12, 23-29, and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the title be amended to recite the method being claimed.

Claim rejections-35 USC § 101/35 USC § 112, first paragraph

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The instant application has provided a description of an isolated DNA encoding a GDF-12 protein and the GDF-12 protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance.

The specification asserts that the invention has utility in that the GDF-12 protein is expected to have TGF-β like activities based on its structural similarity with known members of this family (see Figure 4).

For example, the specification asserts that:

"The TGF-β superfamily consists of multifunctional polypeptides that control proliferation, differentiation, and other functions in many cell types. Many of the peptides have regulatory, both positive and negative, effects on other peptide growth factors. The structural homology between the GDF-12 protein of this invention and the members of the TGF-β family, indicates that GDF-12 is a new member of the family of growth and differentiation factors. Based on the known activities of many of the other members, it can be expected that GDF-12 will also possess biological activities that will make it useful as a diagnostic and therapeutic reagent. (page 5, lines 9-17).

The assertion that the disclosed GDF-12 protein has biological activities similar to known polypeptides in the TGF-β family cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities.

Cytokine or growth factor polypeptide families are known in the art to have different biological activities, despite a close structural relationship. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth

factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et a1., 1998, Development 125:1591-1598, see Abstract and pp. 1594-1596).

In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β; family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36).

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality for new members of cytokine or growth factor polypeptide families, the assertion that the GDF-12 polypeptide recited in the claims has activities similar to previously characterized TGF-β polypeptides is not

substantial. Significant further research would have been required of the skilled artisan to characterize the polypeptide of SEQ ID NO: 12 to determine its particular biological activities or other specific utilities.

In view of the evidence in the art that structural similarity between soluble polypeptides like interleukins, as well as other cytokines and growth factors, cannot accurately predict functional similarity, there is also no well-established utility for the GDF-12 protein and therefore, no well-established utility for using the GDF-12 antibody in the claimed method.

The specification asserts several utilities for GDF-12 that are not necessarily related to its biological activities; however, none of these asserted utilities meets the three-pronged test of being credible, specific and substantial. Each will be addressed in turn:

a) *GDF-12 can be used in therapy*: This asserted utility is credible, but it is not specific or substantial. In particular, the specification states at page 5, lines 18-29, and page 6, lines 1-3 that: "In particular, the expression pattern of GDF-12 suggests that GDF-12 possesses activities that will make it useful for the treatment of various diseases involving the liver. For example, when GDF-12 functions to stimulate the growth or differentiation of liver cells, GDF-12 could be used for the treatment of disease states in which the function of the liver is compromised, such as in hepatitis or cirrhosis. Although liver tissue has the capacity to regenerate, GDF-12 could potentially accelerate the normal regenerative process or promote the process in disease states in which the regenerative process is suppressed. Similarly, GDF-12 could be useful for maintaining liver cells or tissue in culture prior to transplantation or for stimulating the growth of liver cells following transplantation, in this regard, because liver cells may be used as a vehicle for

delivering genes to liver for gene therapy, GDF-12 could be useful for maintaining or expanding liver cells in culture during or after the introduction of particular genes or for stimulating the growth of these cells following transplantation."

Additionally, on page 6, lines 4-16, the specification states:

"Alternatively, when GDF-12 functions as a growth inhibitor, GDF-12 could be used to create cell proliferative disorders involving liver cells, such as hepatocellular carcinoma. Indeed, one member of this superfamily, namely, inhibin alpha, has been shown to function as a tumor suppressor gene, and another member of this superfamily, namely, Mullerian inhibiting substance, has been shown to be capable of inhibiting the growth of tumor cells both in vitro and in vivo.

This high specificity of GDF-12 expression also suggests potential applications of GDF-12 as a diagnostic tool. In particular, because GDF-12 encodes a secreted factor, levels of GDF-12 could be used to monitor liver function or to detect the presence of neoplasms involving liver cells. In this regard, another member of this family, namely, inhibin, has been shown to be useful as a marker for ovarian granulosa cell tumors."

but the specification does not state whether the level of GDF-12 is increased or decreased in malignant cells or disclose that GDF-12 antibodies can be used to detect increased or decreased GDF-12 expression in malignant liver cells. The specification provides no clear nexus between any particular malignant cell and any specific change in GDF-12 form or quantity. Since significant further research would be required before GDF-12 could be used in a real-world treatment method for detection of a specific disease, the asserted utility is not a substantial or specific assertion of utility.

b) *GDF-12 can be used to make antibodies, and the antibodies can be used to identify GDF-12.* This asserted utility is credible, but not specific or substantial. Antibodies can be made from any protein. Also, there is no indication of how to use the antibodies in a real-world use.

Therefore, since the specification does not disclose a specific, substantial and credible utility for the GDF-12 polypeptide, the instant method claims are rejected under 35 U.S.C. 101 for lack of utility.

Claims 15-18 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to practice the claimed invention.

Claim rejections-35 USC § 112, second paragraph

4. Claims 15-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is rejected as vague and indefinite because the method claim fails to recite steps. The result step is unclear from the method claim because the claim fails to recite whether expression of GDF-12 protein is increased or decreased in malignant cells.

Claim 15 is rejected as vague and indefinite for reciting the phrase "having" because it is unclear whether the recitation of "having" is open or closed language. It is suggested that the claim be amended to recite the closed language "consisting of".

Claim 16 recites the limitation "cell". There is insufficient antecedent basis for this limitation because claim 15, line 2, recites “cells”.

Claims 17-18 are vague and indefinite insofar as they depend on claim 15 for its limitations.

Conclusion

No claim is allowed.

Claims 15-18 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

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Primary Examiner
Art Unit 1646
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